Replacing Food Grade Celite® Media with AW Celite NF Media in CGMP Pharmaceutical Processes

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Summary

This technical note summarizes change-control factors with converting from a conventional "Food Grade" to a high purity "NF Grade" Celite media. The similarities and differences between these grades, as they relate to biologic and synthetic processes, are described to assist the reader in formulating a change control strategy consistent with regulatory standards.

NF Grades of Celite media are intended as a direct replacement for Food Grade Celite media.

Background

Diatomite filter aids, which are composed of diatoms (Figure 1), are widely used in CGMP pharmaceutical filtration processes. Recent studies on diatomite quality are driving a change to High Purity filter aid grades[1].

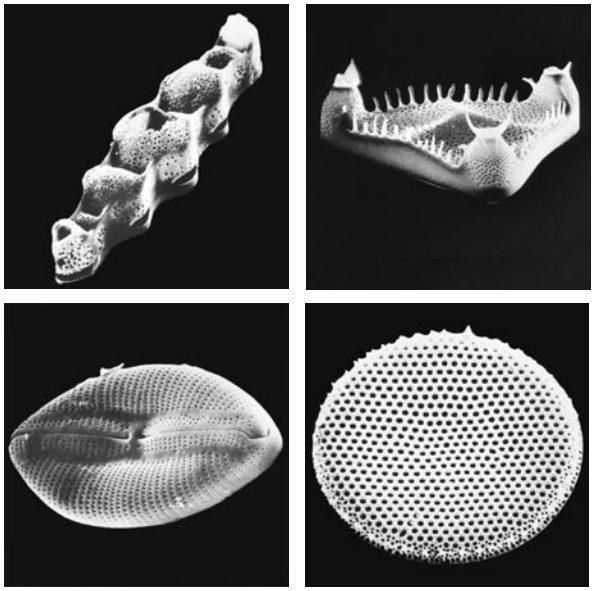

Figure 1. Typical shapes of diatoms (10–200 µm in diameter).

A change of filter aid requires consideration of the FDA change control guidelines[2,3]. These state that a change must first be evaluated for the potential to influence the "identity, strength, quality, purity, or potency" of the drug product. This change must then be classified as "Major, Moderate, or Minor", depending on the potential to impose an "adverse effect on the safety or effectiveness" of the drug product.

These guidelines acknowledge that process changes with licensed products are "frequent" and offer examples of changes and the corresponding classifications. Based on this information, and as the world's largest producer of diatomite filter aids, World Minerals believes that a change from Food Grade Celite media to a NF Celite media may be classified as Minor or Moderate.

This reasoning is based on the fact that NF Celite grades, which carry a similar name to their Food Grade versions (Table 1), are similar to Food Grades in all aspects except for purity.

AW Celite® NF Grade (High Purity)	Permeability (Darcy)	Solids Removed (micron)*
Standard Super-Cel®	0.30	1.2
512	0.40	1.5
Hyflo Super-Cel®	1.0	2.0
503	1.6	3.0
535	3.0	3.5
545	4.0	4.5

** Data is provided for comparison purposes only. Depending on the compressibility of the solids, values may vary from those in the table.*

Table 1. Celite® NF Grades. Note that the names are identical to the conventional versions, except for the AW-NF designation.

1 *Diatomite Filter Aid in CGMP Pharmaceutical Processing, A Regulatory Perspective.*
2 *Guidance for Industry: Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture,* July 2001.
3 *Guidance for Industry: Changes to an Approved NDA or ANDA,* November 1999.

Except for a final purification and packaging steps, the Celite NF grades and Food Grades (both manufactured by Celite Corporation) have identical manufacturing processes. This ensures that the two grades have similar physical properties, such as solid-state chemistry, density, surface area, and permeability.

To assist the reader in formulating a change control strategy, the notable differences between NF Celite media and Food Grades are discussed below.

Final Manufacturing Steps and Packaging

The differences between NF and Food Grade Celite media begin with a purification step. Food Grade Celite is transferred from to our pharmaceutical production facility. The material is subjected to a proprietary purification followed by thorough rinsing with deionized water. The product is then dried and packaged in Tyvek®[4] bags in an enclosed packaging station. These final steps serve three main purposes:

- Removal of extractable impurities
- Packaging of the product in a controlled environment
- Stability of product after storage

Except for purity (see Product Purity), these changes have no practical impact on the filtration performance.

Product Consistency and Documentation

During production, NF Celite media is tested every 100 kg of production with an extensive set of release tests. Food Grade Celite products, in comparison, may be tested as infrequently as every 10,000 kg, with fewer release tests (Table 2).

Parameters	AW Celite Hyflo Super-Cel® NF (High Purity grade)	Celite Hyflo Super-Cel® (Food Grade)
Centrifuged wet-density	≤ 0.37 g/cm^3	≤ 0.35 g/cm^3
Resistivity	≥ 50,000 ohms	*
150 Mesh Screen	≤ 9.5 %	≤ 12 %
USP-NF		
Loss on Drying	≤ 0.5 %	*
Loss on ignition	≤ 2.0 %	*
Leachable arsenic	≤ 10 mg As/kg	*
Leachable lead	≤ 10 mg Pb/kg	*
Water-soluble substances	≤ 0.2 %	*
Acid-soluble substances	≤ 2.0 %	*
Nonsiliceous substances	≤ 25 %	*
** No release specification*		

Table 2. Comparison of release specifications for NF Grade and Food Grade Celite media.

The final production steps, beginning with the acid wash, are supported with auditable batch records, which are not available with Celite Food grades.

These batch records and extra tests eliminate common filtration process deviations associated with conventional diatomite, such as variations in filtrate color, and pH.

Product Purity

There are measurable purity differences between NF Celite and Food Grade Celite media. These include:

- Bulk Chemistry
- Extractables and pH

BULK CHEMISTRY

As can be seen in Tables 3a–3c, there is a small difference in the bulk chemistry between NF and Food Grade Celite media (1.5-3% SiO_2). This is achieved with the acid washing step, which is designed to remove extractable impurities. This leaves the NF Celite diatoms with a similar solid state chemistry to its Food Grade counterparts.

EXTRACTABLES AND pH

The study summarized in Tables 3a–3c shows that when converting from a Food Grade to an NF grade, a relatively small change in bulk chemistry of 1.5-3% SiO_2 can reduce extractables by 60-80%.

This reduction in extractables may have an effect on the process pH. In general, NF Grades will not change the pH of unbuffered solutions; however, the extractables from Food Grades can cause substantial shifts.

These two points (extractables and pH) are the major differences between these grades. Therefore, change studies should address these as the primary determining factors of change classification.

4 This material is supported with a Drug Master File. Tyvek is a registered trademark of DuPont.

TABLES 3a–3c

These tables detail the bulk chemistry and extractables of Food Grade and Celite NF Grades. The products in this study were selected to represent the entire range of products listed in Table 1. Where the data field is blank, no data was generated.

Bulk chemistry by X-ray fluorescence. Extractable analysis by ICP-MS except for Fe (colorimetric complex with 1,10-phenanthroline). Extractables expressed as mg/kg of filter aid extracted from 2-g samples incubated in 100-mL solutions. Solution: 10 mg/mL albumin, 50 mM sodium acetate, pH 4.3. Incubation: 4 h, 160 rpm, 50°C.

	Celite Standard Super-Cel® (Food Grade)		AW Celite Standard Super-Cel® NF	
	Bulk Chemistry (%)	Extractables (mg/kg)	Bulk Chemistry (%)	Extractables (mg/kg)
SiO_2	91.1		92.6	
Si		103.0		144.0
Al_2O_3	4		3.4	
Al		84.1		0.4
$Na_2O + K_2O$	1.1		1.1	
Na				
K		150		20.5
Fe_2O_3	1.3		1.3	
Fe		20.0		1.4
MgO	0.6		0.5	
Mg		50.5		7.4
CaO	0.5		0.3	
Ca		52.5		Below Limit
Cr				
Cr		0.2		0.1
Cu				
Cu		0.8		0.6
TiO_2	0.2		0.2	
Ti		2.3		Below Limit
P_2O_5	0.2			
P		53.0		10.0
Totals	**99.0%**	**516 mg/kg**	**99.4%**	**184 mg/kg**

Table 3a.

	Celite® 535 (Food Grade)		AW Celite® 535 NF	
	Bulk Chemistry (%)	Extractables (mg/kg)	Bulk Chemistry (%)	Extractables (mg/kg)
SiO_2	89.6		92.5	
Si		92.0		52.0
Al_2O_3	4.0		3.0	
Al		11.5		0.6
$Na_2O + K_2O$	3.3		2.5	
Na				
K		29.5		8.0
Fe_2O_3	1.3		1.0	
Fe		22.8		2.2
MgO	0.6		0.4	
Mg		62.5		4.8
CaO	0.5		0.3	
Ca		78.5		Below Limit
Cr				
Cr		8.4		0.2
Cu				
Cu		1.05		0.25
TiO_2	0.2		0.1	
Ti		6.1		Below Limit
P_2O_5	0.2		0.2	
P		35.0		Below Limit
Totals	**99.7%**	**345 mg/kg**	**100%**	**68 mg/kg**

Table 3c.

	Celite Hyflo Super-Cel® (Food Grade)		AW Celite Hyflo Super-Cel® NF	
	Bulk Chemistry (%)	Extractables (mg/kg)	Bulk Chemistry (%)	Extractables (mg/kg)
SiO_2	88.5		89.4	
Si		95.0		55.5
Al_2O_3	3.5		3.4	
Al		18.4		1.4
$Na_2O + K_2O$				
Na	4.1		3.8	
K	0.7	49.5	0.6	17.5
Fe_2O_3	1.5		1.3	
Fe		30.7		1.4
MgO	0.7		0.6	
Mg		59.0		3.4
CaO	0.6		0.5	
Ca				
Cr				
Cr		11.2		0.1
Cu				
Cu		1.35		0.5
TiO_2	0.2		0.2	
Ti		6.4		Below Limit
P_2O_5				
P		59.0		30.5
Totals	**99.8%**	**330 mg/kg**	**99.8%**	**110 mg/kg**

Table 3b.

Further Study

When considering a change from Food Grade to NF Celite grades, it is recommended that the reader contact Advanced Minerals. In most cases, Advanced Minerals can design and conduct (in-house or at your facility) the necessary studies with either in-process or model-process material.

Glossary

COMPONENT
Any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product, 21CFR210.3 (3).

DIATOM
See Diatomite.

DIATOMITE
Obtained from diatomaceous earth, a sediment greatly enriched in biogenic silica in the form of siliceous shells of diatoms, a diverse array of microscopic, single-cell algae. Diatomite products are characterized by an inherently intricate and highly porous structure composed primarily of silica.

FILTER AID
Inorganic mineral powders or organic fibrous materials, used in combination with filtration hardware to enhance filtration performance. Commonly encountered filter aids include diatomite, perlite, and cellulose. Some of these materials have been in use as filter aids for over 75 years.

PERMEABILITY
For use in filtration, diatomite products are usually processed to provide a range of filtration rates that are closely related to their permeability reported in units of Darcies. Diatomite filter aids are available in a wide range of permeabilities. The selection of a filter aid with a particular permeability suitable for a specific filtration process depends on the flow rate and degree of fluid clarification desired for the particular application.